## REMARKS

Claims 1-29 were present in the application as filed. In response to a Restriction Requirement dated October 22, 2002, Applicant elected the claims of Group I, claims 1-13 and 28. Claims 1-29 were therefore, pending in the application with claims 14-27 and 29 withdrawn from consideration. Claims 2, 5, and 7 are canceled above and new claims 30-32 presented. Claims 1, 3-4, 6, 8-13, 28 and 30-32 are pending in the application.

Enclosed herewith is a newly executed Declaration and Power of Attorney. The newly executed Declaration and Power of Attorney contains corrections, however, these have been duly initialed and dated in accordance with 37 C.F.R. §1.52(c).

Independent claim 1 is amended above to clarify the structure of the recombinant protein of the invention as including a target protein of interest that is to be purified and crystallized and a linker. Support for the amendment is found in paragraph [0069] on page 19 of the specification and in now canceled claim 2.

New claims 30-32 are presented. Support for the amendment is found in the specification in paragraph [0039] on page 11. No new matter is presented by the amendments.

### Rejections under 35 U.S.C. §112, second paragraph

Claims 10 and 12 are rejected under 35 U.S.C. §112, first paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action states that claim 10 is indefinite in that it is unclear what is the intended scope of the recitation of "immunologically relevant receptor." Claim 10 is amended herein to recite "...a receptor associated with neuronal or immunologic function" rather than "an immunologically relevant receptor." Applicants believe that it would

be clear to one of skill in the art which receptors are associated with immunologic function (e.g. T-cell receptor, B-cell receptor, receptors for CD4, CD8 etc.)

In as much as claim 1 has been amended above to include (c) a linker, the pendency of claim 12 from claim 11 which depends from claim 1 is no longer inaccurate.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-10, 12, 13, and 28 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 is amended above to recite a recombinant protein comprising:

(a) a first protein that is a motor domain of myosin or an analog, fragment or derivative thereof;

(b) a target protein of interest, the purification and crystallization of which is desired; and

(c) a linker between (a) and (b).

Applicants respectfully submit, that in view of the above amendment, the rejections under 35 U.S.C. §112, first paragraph are moot and should be withdrawn.

A detailed description of the expression, purification and subsequent crystallization, crystallographic analysis and structure refinement of one embodiment of the invention appears in paragraphs [0094] to [0103] of the specification, pages 25-28. Additionally, Table 1 on page 29 of the specification provides further examples of various fusion proteins of the invention that Applicants generated and had undergone various degrees of testing prior to the time the application was filed.

Table 1 demonstrates that Applicants successfully transformed cells with 15 constructs containing a catalytic domain of myosin linked to a protein of interest. Furthermore, of the 15 successful transformations, all but two were tested for expression; nine of the 13 were found to be expressed. Hence, Applicants success rate in expressing a recombinant protein of the invention was nearly 70%.

Additionally, Applicants attempted to purify five of the original 11 proteins successfully expressed; four of the five were successfully purified (i.e., 80%). Finally, Applicants crystallized two of the four purified proteins and solved their structures. Applicants respectfully submit that this represents a representative number of recombinant proteins as claimed in independent claim 1, as amended herein and that, therefore, the examples of recombinant proteins (as shown in Example I and Table 1) generated by Applicants are sufficient to show that Applicants did in fact have possession of the claimed invention at the time the application was filed. Furthermore, the specification contains ample guidance for one of skill to produce the recombinant protein of claim 1, as amended, without undue experimentation. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. 102

Claims 1, 2, 5-7, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Finer et al. (U.S. Patent 6,410,254).

Claim 1 as amended, recites a recombinant protein comprising: (a) a first protein that is a motor domain of myosin or an analog, fragment or derivative thereof; (b) a target protein of interest, the purification and crystallization of which is desired; and (c) a linker between (a) and (b).

Finer et al. teach a method for the identification of candidate agents that bind to a target protein or serve as modulators of the biological activity of a target protein (col. 3, lines 47-50). The "target protein" taught by Finer et al. is undoubtedly kinesin with suitable kinesins being enumerated at column 4, lines 46-52. No specific myosins are taught by Finer et al. as being useful in practicing the method of the invention.

Included in Finer's definintion of "target protein" are various derivatives of kinsein, including fusion of a target polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind (col. 8, lines 56-63). Finer's reference to "fusion proteins" and linkers can only be viewed as gratuitous, since no actual embodiment of such a fusion protein is disclosed. Finer et al., therefore, do not teach a fusion protein having a catalytic domain of myosin, linked via an oligopeptide linker to a target protein of interest, the purification and crystallization of which is desired.

Hence, Applicants respectfully submit that Finer et al. do not teach or fairly suggest Applicants' claimed fusion protein. Withdrawal of the rejection is respectfully requested.

Claims 1, 4-7, 9, 10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurzawa et al. (*Biochemistry* 36: 317-323). Kurzawa teach that C-terminal extension of M761 with one or two α-actinin repeats has very little effect on M761 behavior. While Kurzawa et al. demonstrate that production of a fusion protein is possible, Kurzawa et al. clearly do not teach that the fusion protein comprises myosin linked via an oligopeptide linker to a target protein of interest, the purification and crystallization of which is desired. Thus, Kurzawa et al. do not teach nor fairly suggest Applicants' claimed fusion protein. Withdrawal of the rejection is respectfully requested.

Claims 1, 4-7, 9, 10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332). Manstein et al. teach a rapid method for the purification of large quantities of recombinant myosins. The two-step protocol consists of a myosin specific enrichment of a recombinant myosin protein by binding of the protein to actin followed by $Ni^{2+}$-NTA chromatography. The method and compositions taught by Manstein, however, do not envision a fusion protein comprising a component, the purification and crystallization of which is desired. Thus, Manstein et al. do not teach nor fairly suggest Applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by Lesburg et al. (*Nat. Struc. Biol.* 6: 937-943). Lesburg et al. teach the crystallization of a recombinant RNA-dependent RNA polymerase from hepatitis C virus fused to a hexahistidine oligopeptide. Clearly, by virtue of the amendment to claim 1 herein, claim 28, which is dependent from claim 1 and therefore contains all the limitations of claim 1, is not taught or suggested by Lesburg et al. Withdrawal of the rejection of claim 28 is respectfully requested.

Rejections under 35 U.S.C. 103

Claims 3, 4, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finer et al. The Office Action states that the use of oligopeptide linkers for joining two proteins in a fusion protein was well known to one of ordinary skill in the art. The Office Action further cites Bulow et al. (*Trends Biotech* 9:226-231) as teaching the use of peptide linkers and specifically using linkers that are short as being optimal since longer linkers are often prone to proteolytic cleavage.

As discussed above, Finer et al. do not teach a fusion protein having a catalytic domain of myosin, fused with a target protein of interest, the purification and crystallization of which is desired. Bulow et al. teach the use of linkers in the preparation of bifunctional or polyfunctional

enzymes using gene fusion proteins. Bulow teaches the importance of creating physical proximity to mimic the addition of multiple enzymes to a reaction mixture. "Proximity between two or more enzymes may also be achieved by making an in frame gene fusion of the corresponding structural genes. The chimaeric gene then encodes a polypeptide chain carrying two or more active centers," i.e. a multifunctional enzyme (p.227, 1st col. 1st full paragraph). Hence, Bulow is concerned about the length of the linker both to maximize proximity of the fused polypeptides and the avoidance of proteolytic degradation which would result in separation of the functional sites.

Applicants have designed a fusion protein that facilitates the purification and crystallization of the target protein of interest. Two aspects of the intended function of the recombinant protein of the present invention are significant. Firstly, in order to provide fusion proteins for crystallization purposes, the introduction of a linker sequence is important to prevent any transfer of conformational energy between the two domains. The linker has to be chosen, therefore, with a view to ensuring that any transfer of conformational energy between the domains is avoided during the crystallization process during which crystal order has to be established and any structural alterations of the protein should be avoided.

Furthermore, unlike Bulow, the specification of the present invention teaches that a particularly preferred linker is one that contains a proteolytic cleavage site (paragraph [0039] on page 11. Thus, one of skill in the art would not have been motivated to rely on the teachings of Bulow with respect to a linker for use in preparing a fusion protein of the present invention, i.e. one containing a target protein of interest the purification and crystallization of which is sought.

Thus, Applicants contend that one would not be motivated to combine the teachings of Finer et al. and Bulow et al. In any event, the teachings of Finer et al. and Bulow et al. either individually or in combination result in Applicants' invention as encompassed by amended claim 1. Withdrawal of the rejection is respectfully requested.

Claims 2, 3, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurzawa et al. in view of Bulow et al. As discussed above, Kurzawa et al. do not teach the recombinant protein of claim 1, as amended because it does not contain a linker. Furthermore, as discussed above, the teaching of Bulow et al. is with respect to a linker, the purpose of which is to maintain proximity of the fusion partners so as to achieve a single molecule with bi- or polyfunctionality. Neither reference provides the motivation to insert a linker into the fusion protein of Kurzawa to come up with Applicants' recombinant protein since the reasons for providing a linker, i.e. to prevent transfer of conformational energy between the domains thereby facilitating crystallization of the target protein, was not envisioned by either reference. Therefore, it would not have been obvious to one of skill to combine the cited references.

Claim 11 is rejected under 35 U.S.C.§103(a) as being unpatentable over Kurzawa et al. in view of Van Dijk et al, Ponomarev et al., Furch et al., and Van Dijk et al. Claim 11 is dependent from and therefore, includes all the limitations of amended claim 1. Again none of the cited references either individually or in combination teach a recombinant protein comprising a myosin fragment linked via a oligopeptide linker to a target protein the purification and crystallization of which is ultimately desired.

Claims 2, 3, 8 and 12 are rejected under 35 U.S.C.§103(a) as being unpatentable over Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332) in view of Manstein et al. (*Gene* 162: 129-134). The Office Action states that Manstein et al. (*Gene* 162: 129-134) teach an expression vector with two restriction sites, KpnI and SacI, followed by nucleotides encoding Leu-Gly-Ser followed by XhoI and NsiI restriction sites and that since argos discloses the advantages of using a linker comprising Gly, Ser, and Thr as a preferred linker, it would have been obvious to one of ordinary skill in the art to combine the teaching of Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332) and Manstein et al. (*Gene* 162: 129-134) for constructing an expression vector by inserting a nucleic acid encoding M754 into either the KpnI or SacI sites of pDXA-3H and inserting a nucleic acid encoding the alpha actinin repeat into the XhoI and NsiI restriction sites

of pDXA-3H to generate the fusion protein of Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332) with a linker comprising Leu-Gly-Ser in order to exploit the presence of restriction sites within vector pDXA-3H and to have a fusion protein with a linker comprising Gly and Ser as taught by Argos.

As discussed above, Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332) teach a rapid method for the purification of large quantities of recombinant myosins for the study of the structure and function of myosin. Manstein et al. (*Gene* 162: 129-134) teach the vectors designed to accomplish this goal. Neither reference contains any suggestion regarding the desirability of making a recombinant protein comprising a myosin head fragment linked to a target protein of interest that could be used to facilitate the purification and crystallization of the target protein of interest.

The problem with the Examiner's determination of obviousness is that there is no basis in the cited art for modifying the fusion protein of Manstein et al. (*J. Mus. Res. Cell Mot.* 16: 325-332). In *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) the court held that "While the court appreciates the commissioner's thorough explanation...., the commissioner's brief is not prior art... The prior art does not indicate...the relationship. [W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the reference." The Examiner has used Applicants' own disclosure of their invention as the blueprint and has constructed an obviousness rejection by hindsight. The courts and the PTO Board of Appeals have cautioned against this temptation on numerous occasions. See, for example, *Ex parte Dussaud*, 7 USPQ2d 1818, 1820 (1988) wherein the Board stated, "The mere fact that the prior art could be modified in the manner proposed by the Examiner would not have made the modification obvious unless the prior art suggested the desirability of the modification." See also *Ex parte Clapp*, 227 USPQ 972 973 (1985), wherein the Board stated "[S]implicity and hindsight are not proper criteria for resolving the issue of obviousness." In the present case, both Manstein et al. references are concerned with the improved production and purification of recombinant myosin products

wherein increased quantities of myosin proteins are useful in studying the structure and function of myosin; they say nothing about producing a fusion protein of myosin and a target protein of interest, wherein the fusion protein is useful in facilitating purification and crystallization of the target protein of interest.

The combination of the cited references, does not, therefore, teach or fairly suggest the recombinant protein of claim 1 as amended herein. Withdrawal of the rejection is respectfully requested.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. The dependent claims are believed allowable for the same reasons as the independent claims from which they ultimately depend, as well as for their additional limitations. Should the Examiner require clarification of any of the above, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date of signature: August 25, 2003

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